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# Guidance for Industry ANDAs: Stability Testing of Drug Substances and Products

## Questions and Answers

### ***DRAFT GUIDANCE***

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**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)**

**August 2013  
Generics**

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# Guidance for Industry ANDAs: Stability Testing of Drug Substances and Products

## Questions and Answers

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**U.S. Department of Health and Human Services  
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# **Guidance for Industry<sup>1</sup>**

## **ANDAs: Stability Testing of Drug Substances and Products**

### **Questions and Answers**

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

#### **I. INTRODUCTION**

This draft guidance provides answers to questions from the public comments we received on the draft guidance for industry on *ANDAs: Stability Testing of Drug Substances and Products* (stability guidance) that published on September 25, 2012. The final guidance for industry of the same title published on June 20, 2013. General issues; drug master files (DMFs); drug product manufacturing and packaging; and stability studies are discussed in this guidance and are intended to clarify the stability testing data recommendations for abbreviated new drug applications (ANDAs). In this document, the terms drug substance and active pharmaceutical ingredient (API) are used interchangeably.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

#### **II. QUESTIONS AND ANSWERS**

##### **A. General**

***Q1: What is the scope of and implementation date for the stability guidance?***

**A1:** The stability guidance covers all new ANDAs under the Federal Food, Drug, and Cosmetic Act, section 505 (j), and DMFs (Type II for drug substances that support the ANDAs). It does not apply to postapproval changes. The final

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<sup>1</sup> This guidance has been prepared by the Office of Generic Drugs, Office of Pharmaceutical Science in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

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guidance availability will be announced in the Federal Register. The implementation date is June 20, 2014.

***Q2: How will this guidance affect the President’s Emergency Plan for AIDS Relief (PEPFAR) and positron emission tomography (PET) ANDAs?***

A2: For chemistry, manufacturing, and controls (CMC) information, PEPFAR ANDAs should follow the guidance for industry on *Fixed Dose Combinations, Co-Packaged Drug Products, and Single-Entity Versions of Previously Approved Antiretrovirals for the Treatment of HIV*.<sup>2</sup>

For PET ANDAs, the Agency recommends a minimum of three batches at or near the upper end of the proposed radio-concentration. If different synthesizers (methods of synthesis) are used, three batches from each method of synthesis at or near the upper end of the proposed radio-concentration are recommended. Batches do not have to be made in the same facility. For the additional manufacturing facilities, applicants should provide stability data on at least one batch from each facility, although bracketing approaches could be submitted for review. For additional information, the Agency has published a guidance for industry on *FDA Oversight of PET Products, Questions and Answers*.

***Q3(i): Can an ANDA be submitted with 6 months of accelerated stability and 6 months of long-term stability data?***

A3(i): Yes. Stability data expectation at the time of ANDA submission is 6 months of accelerated and 6 months of long-term data. However, if 6 months accelerated data show significant change<sup>3</sup> or failure of any attribute, 6 months of intermediate data are also recommended at the time of submission.

***Q3(ii): When do intermediate stability studies need to be initiated in the event of failure at accelerated condition?***

A3(ii): We recommend starting intermediate stability, accelerated, and long-term studies at the same time so the data are available at the time of submission, if needed.

***Q3(iii): If one among the three batches in accelerated conditions show a significant change, what should be done?***

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<sup>2</sup> We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

<sup>3</sup> See the International Conference on Harmonisation (ICH) guidance to industry on *Q1A(R2) Stability Testing of New Drug Substances and Products*, section 2.2.7.1.

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A3(iii): In the event accelerated data show significant change or failure of any attribute in one or more batches, intermediate data is recommended for all three batches.

***Q4: Can stability bracketing and/or matrixing be used to determine the configurations to be placed on stability for an original ANDA without prior approval from the Office of Generic Drugs (OGD)?***

A4: Yes. You should follow the International Conference on Harmonisation (ICH) guidance for industry on *Q1D Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products* and its example tables.

***Q5(i): If an application that qualifies for the Generic Drug User Fee Act (GDUFA) 10-month review is filed with 6 months of accelerated and 6 months of long-term data, and there are no blocking patents or exclusivities, will 24 months of expiration dating be granted?***

***Q5(ii): During the review cycle, will the application need to be updated with 12 months of long-term data?***

A5(i,ii): FDA will grant a proposed expiry period of two times the available long-term data at the time of approval (up to 24 months) following the ICH *Q1E Evaluation of Stability Data* (ICH Q1E) guidance, provided the submitted data are satisfactory, and data evaluation is provided in accordance with ICH Q1E. Please refer to the decision tree (Appendix A) in ICH Q1E. The ANDA should be updated with 12 months of long-term data.

***Q6: Can only two lots of finished product at pilot scale batch size ever be sufficient to support the stability of an ANDA for simple dosage forms?***

A6: No. You should follow the recommendations in the stability guidance where three pilot scale batches or two pilot scale batches and one small scale batch are recommended. This applies to all dosage forms.

***Q7: How is the proposed expiration date supposed to be calculated? Will 6 months of accelerated data equal 24 months at long-term?***

A7: ICH Q1E principles will help in the calculation of expiration dating. Data from the three ANDA submission batches (i.e., 6 months), accelerated data meeting all criteria (without significant change per ICH Q1A(R2)), and 12 months long-term data without variability will not need statistical evaluation. Stability data from three ANDA submission batches at 12 months long-term are recommended for 24-month extrapolation.

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If there is a significant change in the accelerated data, ICH Q1E, Appendix A, provides more detail regarding when intermediate condition stability data are recommended.

***Q8: For 6 months accelerated data, will 24 weeks be the timeframe required because 12 weeks is accepted as equivalent to 3 months?***

A8: No. The ICH stability guidances have indicated time recommendation only in terms of months.

***Q9: When a patent is due to shortly expire and there are no approved ANDAs, can we file with 3 months stability data with a commitment to supply 6 months data when available?***

A9: No. ICH stability guidances should be followed regardless of patent status; 6 months of accelerated data are recommended at the time of filing the ANDA.

***Q10: How long do the three pilot scale batches, submitted as a part of an ANDA, need to be stored before destruction?***

A10: Sample storage times are discussed in 21 CFR 320.38 and 21 CFR 320.63 for bioequivalence-study-samples when the pilot scale batch is used in the bioequivalence study or studies. In addition, the guidance for industry on *Handling and Retention of BA and BE Testing Samples* may be helpful. In general, ANDA submission batch samples should be stored for 1 year after approval of the ANDA, and samples of the drug product used for bioequivalence studies should be stored following requirements listed in the CFR citations and recommendations in the guidance listed above.

### **B. Drug Master File**

***Q1: Please clarify the effect of the stability guidance on Drug Master File (DMF) holders.***

***Q1(i): Are stability data from three current good manufacturing practice (CGMP) batches required to be filed in the DMF to support the API retest date?***

A1(i): ICH Q1A(R2) recommends three primary batches<sup>4</sup> (at least of the pilot scale<sup>5</sup> size) for the drug substance filed in the DMF. These batches should be made under Current Good Manufacturing Practices (CGMP). The stability guidance recommends a minimum of 6 months of accelerated and 6 months of long-term data for the pilot scale batches to be submitted initially. Additional long-term data for all three batches, as the data becomes available through the proposed retest period, should be submitted as an amendment.

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<sup>4</sup> Defined in ICH Q1A(R2) Glossary.

<sup>5</sup> Ibid.

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***Q1(ii): How many months of long-term and accelerated data are required when a “Completeness Assessment” is performed on the DMF? Also, what should the DMF stability section contain for the same?***

A1(ii): To pass the Completeness Assessment (see the draft guidance for industry on *Initial Completeness Assessments for Type II API DMFs under GDUFA*), DMFs should have the stability protocol, commitments, and data demonstrating that stability studies have started. The initial and one additional time point for the accelerated studies and long-term studies are sufficient. The DMF holder should amend the DMF with updated stability data to prepare for the full scientific review, if the DMF does not meet the recommendations under A1(i) above at the time of the Completeness Assessment.

***Q2: Will submissions to DMFs be accepted based on stability data from production scale batches?***

A2: Yes. Per ICH Q1A(R2), section II, A, 8, Stability Commitment (2.1.8), the submission is appropriate if satisfactory stability data from three production batches made under CGMP are filed in the DMF with 6 months of accelerated data and long-term data covering the proposed retest period.

### **C. Drug Product Manufacturing and Packaging**

***Q1: Can the split bulk solution filled into different fill volumes be considered different batches?***

A1: No. Split filling one batch of bulk solution into different fill volume sizes does not constitute discrete batches.

***Q2: Can you clarify the packaging recommendations for the submission batches for blow-fill-seal containers?***

A2: Blow-fill-seal containers are not an exception from regular packaging and are usually packaged inside a secondary container or a carton. The secondary packaging should be included in all three batches. ICH Q1A(R2) addresses secondary packaging usefulness (see section II, B, 4, Drug Product Container Closure System (2.2.4)).

***Q3: Should all three batches be stored in final proposed packaging?***

A3: Yes. You should package all three batches in the container closure system proposed for marketing. Q1A(R2) addresses this question (see section II, B, 4, Drug Product Container Closure System (2.2.4)).



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***Q4: What is the Agency's position on using different lots of APIs and/or packaging materials? How many API lots should be used in the manufacture of finished product lots used to support the ANDA?***

A4: A minimum of two lots of the drug substance<sup>6</sup> should be used to prepare the three primary batches of drug product. It is not necessary to use different lots of packaging material, except in cases where the packaging material could affect drug product performance and/or delivery.

***Q5: Should the small scale batches be packaged with commercial equipment, or is it acceptable to package using research equipment or by hand?***

A5: Small scale batches should be packaged with commercial equipment. Packaging systems used should be the same as or similar to packaging proposed for storage and market distribution. Please refer to ICH Q1A(R2) section II, B, 3, Selection of Batches (2.2.3) and the glossary definition for primary batches.

***Q6: What will the recommendation for secondary packaging be?***

A6: We recommend following ICH Q1A(R2) section II, B, 4, Drug Product Container Closure System (2.2.4).

***Q7: What are the recommendations for stability testing of modified release products?***

A7: FDA recommends following the guidance for data on three batches per ICH Q1A(R2). ICH stability guidances do not distinguish among different dosage forms.

***Q8: What are the recommendations for the submission of oral solutions, ophthalmic solutions, oral and ophthalmic suspensions, transdermal patches, ointments, creams, granules for reconstitution, and parenterals?***

A8: Our recommendations follow ICH Q1A(R2), and we recommend three discrete batches and 6 months of accelerated and long-term data at the time of submission for all dosage forms. Also, refer to other questions and corresponding answers that specifically discuss other dosage forms included in this document.

***Q9: Are 6 months of stability data required on all three batches, or would one batch at 6 months and two lots at 3 months be acceptable?***

A9: Following ICH stability guidances, 6 months (accelerated) stability is recommended on all three submission batches.

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<sup>6</sup> For nasal aerosols (meter-dose inhalers) and nasal sprays (meter-dose spray pumps), you should submit three different lots of drug substance.

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***Q10: Should the executed batch records for the three batches be included in the ANDA submission?***

A10: Yes.

***Q11: Does all relevant CMC batch information for the three stability batches need to be included in the application (i.e., excipient Certificate of Analysis (COA))?***

A11: Yes. When more than one lot of API or excipients is used, the corresponding section in Module 3 should contain that information.

***Q12: If you are an applicant submitting an ANDA with two API sources, are you required to perform stability on three batches of drug product for each API source?***

A12: If you propose to add a second or more than two sources of API for the same drug substance, we recommend you provide the following CMC information:

- Comparison and justification of comparability (by the firm) of the physico-chemical properties and impurities of the drug substance from each source.
- Appropriate stability data on three batches of drug product qualifying the first API source used in the bioequivalence (BE) studies as recommended by the stability guidance.
- A single pilot scale batch of the drug product bio-strength(s) manufactured using the second or each of the other proposed API source(s) used to support the ANDA application, along with comparative dissolution data.
- Appropriate stability data (accelerated and long-term for 6 months at the time of filing) on the strength(s) manufactured for each API source. Appropriate stability data may in some cases include intermediate condition stability data.

***Q13: What is meant by “small” scale? “Small” is not a defined word in ICH guidance. What are the packaging expectations from the small batch, as well as from the two pilot scale batches? Traditionally, ANDAs are submitted with 100,000 units for solid oral dosage forms. Is this still applicable?***

A13: The interpretation of what constitutes a small scale batch for the purpose of filing ANDAs is further elaborated below for various dosage forms and their packaging recommendations. Unless specifically noted below, one primary batch should be fully packaged.

### **Oral dosage forms**

**(a) Tablets/Capsules (e.g., immediate release, extended release, chewable, orally disintegrating and delayed release tablets or capsules):** Two of the

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three batches should be of at least 10 percent of the proposed production batch or 100,000 finished dosage units, whichever is greater (i.e., pilot scale batches). The third batch can be smaller than the 10 percent of the proposed production batch, but not less than 25 percent of the pilot scale batch. We recommend stability data be generated for the three ANDA submission batches in the proposed marketing container. A minimum of 100,000 units in all proposed presentations is recommended. Representative samples from all three batches must be packaged in a sufficient number of proposed marketing presentations to comply with 21 CFR 211.166(a)(1-5) and 211.166(b).

**(b) Powders/Solutions/Suspensions:** Two of the three batches should be at least 10 percent of the proposed maximum size commercial batch. The third batch can be smaller than 10 percent of the proposed commercial batch, but not less than 25 percent of the pilot scale batch. To capture variability introduced by packaging, the product from all the batches should be used in the packaging process. We recommend packaging representative samples from all three batches of a sufficient number of proposed marketing presentations to comply with 21 CFR 211.166(a)(1-5) and 211.166(b).

### **Parenterals**

**Solutions/Powders for Solutions (lyophilized cakes)/Suspensions/Sterile Topicals (Ophthalmic and Otic drug products):** Two of the three batches should be at least 10 percent of the proposed maximum size commercial batch (i.e., pilot scale size) or 50 L (per batch), whichever is larger. The third batch can be smaller than 10 percent of the proposed commercial batch, but not less than 25 percent of the pilot scale batch. To capture variability introduced by packaging, the product from all the batches should be used in the packaging process. Representative samples from all the three batches should be packaged in a sufficient number of proposed marketing presentations to comply with 21 CFR 211.166(a)(1-5) and 211.166(b). We recommend manufacturing all the batches to meet sterility requirements.

### **Transdermal Patches**

Two of the three batch sizes for each strength should be at least 10 percent of the proposed commercial production batch or 25,000 units (for each strength), whichever is greater. The third batch can be smaller than 10 percent of the proposed commercial batch, but not less than 60 percent of the pilot scale batch. For transdermal matrix products, where different strengths are identified by the transdermal patch size (surface area), to comply with the three batch size recommendation, we recommend providing data on patches manufactured using three distinct matrix laminates at the time of submission. (Each laminate can be cut to support multiple strengths in the application, where applicable.) We recommend you contact the appropriate review

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division if you are manufacturing transdermal patches using other technologies (e.g., reservoir).<sup>7</sup>

You should include a representative sample from all three batches using different components of backing, adhesives, release liner, and other critical excipients used in packaging a sufficient number of proposed marketing presentations to comply with 21 CFR 211.166(a)(1-5) and 211.166(b).

### **Topicals**

**(a) Creams/Lotions/Gels:** For nonsterile semi-solid dosage forms,<sup>8</sup> the two pilot scale batches should be at least 100 Kg or 10 percent of the production batch, whichever is larger. The third batch can be smaller than 10 percent of the proposed commercial batch, but not less than 40 percent of the pilot scale batch. We recommend packaging representative samples from all the three batches in a sufficient number of proposed marketing presentations to comply with 21 CFR 211.166(a)(1-5) and 211.166(b).

**(b) Inhalation Solutions/Nasal Sprays (nasal nonmetered dose atomizer):** Please refer to the following guidances for industry for information: *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation*, and *Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action*.

Please contact OGD to discuss other dosage forms and/or routes of administration not covered in this document.

**Q14:** *Is it acceptable to use a technical grade of the drug substance for the small scale batches or one of the two pilot scale batches of finished product?*

A14: No. CGMP requirements for ANDA submission are expected for the drug substance and drug product. Because the drug substance quality can affect the drug product stability, the drug substance used for the ANDA batches (supporting the application) should be of the same quality intended for the market product. We would consider data from the use of a different grade drug substance for a product as supporting data. This does not satisfy the submission batch recommendations.

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<sup>7</sup> See the guidance for industry on [Residual Drug in Transdermal and Related Drug Delivery Systems](#).

<sup>8</sup> See the CDER Data Standards Manual, <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/DataStandardsManualmonographs/default.htm>.

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***Q15: Do the small scale batches need to be manufactured in accordance with all CGMP regulations, or is it acceptable to manufacture the small scale batches in a research setting?***

A15: All ANDA submission batches should be made under CGMP.

***Q16: Do the small scale batches need to meet the same finished product specification as the pilot scale batches?***

A16: Yes. The specification should be the same for all three ANDA submission batches.

***Q17: For sterile products, is it acceptable to manufacture the small scale batches in a nonsterile facility and allow variance from sterility and particulate criteria?***

A17: No. Batches should not be manufactured in a nonsterile facility. Sterility is a critical quality attribute (CQA) for sterile products.

***Q18: Do small scale batches need to be produced at the proposed commercial site?***

A18: Yes. The primary batch information submitted in the application is used to support the proposed commercial product manufacture. Product batches produced at a different site than the proposed commercial site would not be considered as primary batches.

***Q19: In cases where an intermediate bulk material is identical between the various strengths (dose proportional blends, bulk solutions, etc.), is it sufficient to perform stability on one lot of each strength, when each strength is produced from a separate intermediate bulk?***

A19: No. For ANDAs that contain multiple strengths (that are dose proportional), three separate intermediate bulk granulations (or blends) should be manufactured. One batch of bulk granulation (or blend) should be used to manufacture all the strengths proposed. The other two bulk granulations (or blends) can be used to manufacture only the lowest and the highest strengths, in addition to the strength used in BE studies. Stability testing should still use all three batches of drug product.

***Q20: What are the exception criteria from meeting the minimum size for pilot scale recommendations for ANDA submission batches? What justification would be needed if we wanted to deviate from the guidance recommendations?***

A20: The submission ANDA batches can have a smaller size than the established pilot scale, according to the ICH definition, when any one of the following circumstances prevails:

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- The reference listed drug product has an orphan drug designation.
- Use of a controlled drug substance is based on a Drug Enforcement Administration allocation.
- The test batch size is the same as the commercial batch size with the commitment that a prior approval supplement (PAS) will be provided when there is a scale-up.

***Q21: Are scale-up and postapproval changes (SUPAC) level one and two variations and changes permitted among the three ANDA submission batches for components and composition?***

A21: No. The three ANDA submission batches should maintain the chosen formula based on product development studies for components and composition.

***Q22: Can some specific examples of cases where statistical analysis is required and type of analysis needed be provided?***

A22: The stability guidance recommends analysis of data in accordance with ICH Q1E, Appendix A. The flowchart in that guidance provides clear situations where analysis is normally recommended or unnecessary. In addition, ICH Q1E B.7 figures provide example diagrams for assay and degradation products that illustrate how plots should be generated for the three batches using regression lines and upper and lower confidence limits.

### **D. Amendments to Pending ANDA Application**

***Q1: What are the recommendations for amendments and responses filed to pending ANDAs after issuance of the new guidance?***

A1: All amendments submitted to pending ANDAs after the effective date of the final stability guidance will be held to the standards in place at the time of the original ANDA submission, unless there is a concern with the submitted stability data.

### **E. Stability Studies**

***Q1: What will be the expected testing time points on accelerated conditions?***

A1: In general, we recommend four time points (i.e., 0 (initial release), 3 months, 6 months, and one additional time point) to the study design for all ANDAs.<sup>9</sup>

***Q2: Can the Agency clarify expectations for the storage positions for products placed into the stability program?***

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<sup>9</sup> This recommendation also applies to nasal spray, inhalation solution, suspension, aerosols, and liposomal drug products.

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A2: For primary batches of liquids, solutions, semi-solids, and suspensions, the product should be placed into both inverted (or horizontal) position and upright (or vertical) position. For routine stability studies, the firm should pick the worst case orientation for the study.

### ***Q3: When and how are reconstitution/dilution studies performed?***

A3: Recommendations listed in Q1A(R2), section II, B, 7, Storage Conditions (2.2.7) should be followed for all three batches. These studies should be performed when the drug product is labeled for reconstitution or dilution.

### ***Q4: What type of containers are classified as semipermeable containers, and can the Agency clarify the stability expectations for the drug products in semipermeable containers?***

A4: Examples of semipermeable containers are provided in the Q1A(R2) glossary. The recommendations for stability expectations for semipermeable containers are detailed in ICH Q1A(R2) section II, B, 7, c. Drug products packaged in semipermeable containers (2.2.7.3).

### ***Q5: Can the Agency clarify expectations around the number of batches to support tests such as preservative effectiveness and extractable leachable testing?***

A5: One of the primary batches of the drug product should be tested for antimicrobial preservative effectiveness (in addition to preservative content) at the end of the proposed expiration dating period. The drug product specification should include a test for preservative content, and this attribute should be tested in all stability studies.

Extraction/leachable studies are generally one time studies; however, if multiple types of containers/closures are employed for packaging, then additional studies could be recommended.

### ***Q6: When are in-use stability studies needed?***

A6: Please refer to response A3 under section E Stability Studies.

### ***Q7: Are there changes to postapproval protocols and commitments when ICH stability guidances are implemented because of scale or type of batches submitted?***

A7: ICH Q1A(R2), section II, B, 8, Stability Commitment (2.2.8) addresses this question. Section 2.1.8 provides information regarding stability commitment for drug substances.

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525 Also, a commitment should be made for ANDAs and DMFs to place one  
526 batch of drug product and substance, respectively, into the annual long-term  
527 stability program, and provide stability data in the annual reports.